REMARKS

Applicant wishes to thank Examiner Sullivan for the courtesy extended to Drs. Bartlett and Moss, inventors, George Pipia, representative of assignee, and Nancy Vensko, attorney of record, on October 20, 2005. The Interview Summary Form PTOL-413 summarizes the discussion held at the personal interview. The present response to the outstanding Office Action includes the substance of the Examiner Interview.

A. Disposition of Claims

Claims 1-13, 15, 17, 18, 25, and 45-50 are pending in this application. The subject matter of the original claims has been reinstated to comply with the new policy recently adopted by the Patent Office that an *in vivo* tumor cell constitutes nonstatutory subject matter, thus the amendment has been made for reasons unrelated to patentability. Support for the amendment is found throughout the specification, for example, in the original claims (directed to compositions of matter), at ¶ 0018 (WR strain), ¶ 0030 (claims 46 and 47), ¶ 0034 (claim 48), ¶ 0035 (claim 49), and Examples 10 and 11 (claim 50). Original claim 14 has been re-written as claim 45, now that the subject matter of the original claims has been reinstated. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

B. Compliance with 35 USC 102 and 103

Due to the reinstatement of the subject matter of the original claims, the rejection of the original claims must be addressed. Beginning with novelty, in the Office Action mailed 20 May 2003, the Patent Office rejected original Claims 1, 2, 5, 6-12, 14, 15 and 25 under 35 USC 102(b) as being anticipated by Bodemer et al. (1991) EP 0 443 335. The Patent Office rejected original Claims 1-9, 12, 15 and 25 under 35 USC 102(b) as being anticipated by Paoletti et al. (1992) WO 92/15672.

Turning to nonobviousness, in the Office Action mailed 20 May 2003, the Patent Office rejected original Claims 1, 2, 5, 6-12, 13, 14, 15 and 25 under 35 USC 103(a) as being unpatentable over Bodemer et al. (1991) EP 0 443 335 and further in view of any one of Lee et al. (U.S. Patent No. 5,851,991), Kamb (U.S. Patent No. 5,739,027), Herlyn et al. (U.S. Patent No. 5,622,835),

Rotter et al. (WO 94/10575) or Spitsberg et al. (WO 98/08394). The Patent Office rejected original Claims 1, 2, 5, 6-12, 14, 15 and 25 under 35 USC 103(a) as being unpatentable over Bodemer et al. (1991) EP 0 443 335 and further in view of any one of JP 55026477, Sawamura et al. (U.S. Patent No. 5,962,260), Cheng et al. EP 0 585 960, Boehmert et al. (DE 3411472), Rasmussen et al. (U.S. Patent No. 5,236,838), Kataoka et al. (JP 020655779), or Cheng et al. (U.S. Patent No. 5,981,714).

Concluding with the Office Action mailed 12 May 2005, the Patent Office rejected examined Claims 1-12, 15, 17, 25 and 27 under 35 USC 103(a) as being unpatentable over Mastrangelo et al. (1995) WO 95/31105 in view of Dorner et al. (U.S. Patent No. 6,103,244) and in view of Buller et al. (1988) J Virol 62: 866. The Patent Office rejected examined Claims 1 and 18 under 35 USC 103(a) as being unpatentable over Dorner et al. (U.S. Patent No. 6,103,244) in view of Buller et al. (1988) J Virol 62: 866, and further in view of Zhang et al. (1996) Biochem Biophys Res Commun 227: 707. The Patent Office rejected examined Claims 1, 12 and 13 under 35 USC 103(a) as being unpatentable over Dorner et al. (U.S. Patent No. 6,103,244) in view of Buller et al. (1988) J Virol 62: 866, and further in view of Paoletti (U.S. Patent No. 5,942,235).

The section 102 issue is whether the claims are in compliance with 35 USC 102 or anticipated by the cited art. The rule according to MPEP 2131 is that to anticipate a claim, the reference must teach every element of the claim. Bodemer et al. (1991) EP 0 443 335 describes a plasmid containing a multiple cloning site (MCS) cloned into the thymidine kinase (TK) locus and use of an attenuated strain that is attenuated by inactivation of the vaccinia growth factor (VGF) gene, but does not experimentally demonstrate that a combined thymidine kinase-negative (TK-) and vaccinia growth factor-negative (VGF-) vaccinia virus can be made. Paoletti et al. (1992) WO 92/15672 describes the NYVAC.2 strain in which both the TK and VGF genes are deleted, in addition to a deletion of a plurality of other genes that would render the strain overly attenuated.

Here, the subject matter of the original claims has been reinstated such that the claims are directed to:

> A composition of matter comprising a recombinant WR strain vaccinia virus, said vaccinia virus comprising a mutation in a thymidine kinase (TK) gene of the genome of said vaccinia virus to produce a negative TK phenotype and comprising a mutation in at least one vaccinia virus growth factor (VVGF) gene of the genome of said vaccinia virus to produce a negative VVGF phenotype.

The claims distinguish over the cited art by virtue of a requirement for a combined TK- and VGF- WR strain. They distinguish over Paoletti et al. (1992) WO 92/15672 because the WR strain does not entail a deletion of a plurality of other genes that would render the strain overly attenuated. Per the experimental section in the instant specification and post-filing date inventor-created art of McCart et al. (Dec 2001) Cancer Res 61: 8751, of record, the claims distinguish over Bodemer et al. (1991) EP 0 443 335 because the combined TK- and VGF- WR strain constitutes experimental proof that such a double deletion vaccinia virus can be made and by use of a specific strain not envisaged by Bodemer et al. in their generic description of an attenuated strain that is attenuated by inactivation of the vaccinia growth factor (VGF) gene.

The section 103 issue is whether the claims are in compliance with 35 USC 103 or unpatentable as being obvious over the cited art. The rule according to MPEP 716.02 is that unexpected results rebut a case of obviousness. Per the experimental section in the instant specification and post-filing date inventor-created art of McCart et al. (Dec 2001) Cancer Res 61: 8751, of record, the results achieved by the present invention are unexpected.

The inventors developed a combined TK- and VGF- vaccinia virus and investigated its properties *in vitro* and *in vivo*. A WR strain vaccinia virus that possessed the lacZ gene inserted into its VGF sites was used as the background virus. A vaccinia shuttle plasmid was created that allowed for homologous recombination of enhanced green fluorescent protein (EGFP) into the TK locus of the background virus creating double-deleted vaccinia virus (vvDD). Infection of resting and dividing cells with vvDD yielded reduced viral recovery compared with wild-type (WT), TK-, or VGF- viruses from resting cultures but equivalent virus recovery from dividing cultures. Tissues and tumor from mice injected with WT, TK-, VGF-, or vvDD vaccinia virus

were harvested for viral titer determination. No virus was recovered from the brains of mice injected with vvDD compared with the other viruses; however, equivalent amounts were recovered from tumor. There was no toxicity from vvDD because mice receiving vvDD lived long-term, whereas mice receiving WT, VGF-, or TK- virus had median survivals of only days. Mice bearing murine colon adenocarcinoma (MC38) had significant tumor regression after treatment with systemic vvDD compared with control. Surprisingly, this antitumor effect is attributable to the replication of virus alone because no therapeutic genes had been included in the treatment. The data demonstrate that a TK- and VGF- vaccinia virus is significantly attenuated in resting cells *in vitro* and demonstrates tumor-specific replication *in vivo*. Thus, the combined TK- and VGF- vaccinia virus is a remarkable vector for use in tumor-directed gene therapy, given its enhanced safety profile, tumor selectivity, and the oncolytic effects after systemic delivery. Taking into consideration these superior advantages, the conclusion is that the claims are non-obvious over the references. Thus, the claims are in compliance with 35 U.S.C. §103(a).

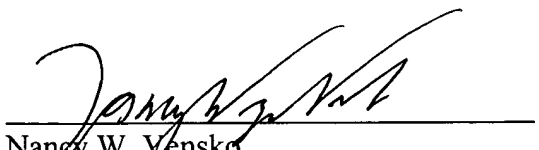
CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/10/05

By: 

Nancy W. Vensko
Registration No. 36,298
Attorney of Record
Customer No. 45,311
(805) 547-5585

2022243
102605